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PTO/SB/21 (04-04)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	09/542,445
Filing Date	April 4, 2000
First Named Inventor	Staples
Art Unit	1645
Examiner Name	S. Devi, Ph.D.
Total Number of Pages in This Submission: 12	Attorney Docket Number: BEH-7354A DIV

ENCLOSURES *(Check all that apply)*

- [xx] Fee Transmittal Form
  - [ ] Fee Attached
- [ ] Amendment/Reply
  - [ ] After Final
  - [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Response to Missing Parts/ Incomplete Application
  - [ ] Response to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Request for Refund
- [ ] CD, Number of CD(s) _____
- [ ] After Allowance communication to Technology Center (TC)
- [ ] Appeal Communication to Board of Appeals and Interferences
- [xx] Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- [ ] Proprietary Information
- [ ] Status Letter
- [xx] Other Enclosure(s) (please Identify below):

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Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm or Individual name	Cynthia G. Tymeson Dade Behring Inc.
Signature	Cynthia G. Tymeson
Date	09/09/04

CERTIFICATE OF TRANSMISSION/MAILING

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Typed or printed name	Cynthia G. Tymeson		
Signature	Cynthia G. Tymeson	Date	09/09/04

PTO/SB/17 (10-03)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

FEE TRANSMITTAL for FY 2004

Effective 10/01/2003. Patent fees are subject to annual revision.

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 330.00

Complete if Known	
Application Number	09/542,445
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METHOD OF PAYMENT *(check all that apply)*

☐ Check ☐ Credit card ☐ Money Order ☐ Other ☐ None

☒ Deposit Account:

Deposit Account Number: 04-0010

Deposit Account Name: Dade Behring Inc.

The Director is authorized to: *(check all that apply)*

☐ Charge fee(s) indicated below ☐ Credit any overpayments

☐ Charge any additional fee(s) or any underpayment of fee(s)

☐ Charge fee(s) indicated below, **except for the filing fee** to the above-identified deposit account.

FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1001	770	2001	385	Utility filing fee	
1002	340	2002	170	Design filing fee	
1003	530	2003	265	Plant filing fee	
1004	770	2004	385	Reissue filing fee	
1005	160	2005	80	Provisional filing fee	

SUBTOTAL (1) ($)

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

	Extra Claims		Fee from below	Fee Paid
Total Claims		-20** =		X =
Independent Claims		- 3** =		X =
Multiple Dependent				=

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
1202	18	2202	9	Claims in excess of 20
1201	86	2201	43	Independent claims in excess of 3
1203	290	2203	145	Multiple dependent claim, if not paid
1204	86	2204	43	** Reissue independent claims over original patent
1205	18	2205	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($)

**or number previously paid, if greater; For Reissues, see above

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1051	130	2051	65	Surcharge - late filing fee or oath	
1052	50	2052	25	Surcharge - late provisional filing fee or cover sheet	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for *ex parte* reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	
1252	420	2252	210	Extension for reply within second month	
1253	950	2253	475	Extension for reply within third month	
1254	1,480	2254	740	Extension for reply within fourth month	
1255	2,010	2255	1,005	Extension for reply within fifth month	
1401	330	2401	165	Notice of Appeal	
1402	330	2402	165	Filing a brief in support of an appeal	330.00
1403	290	2403	145	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive - unavoidable	
1453	1,330	2453	665	Petition to revive - unintentional	
1501	1,330	2501	665	Utility issue fee (or reissue)	
1502	480	2502	240	Design issue fee	
1503	640	2503	320	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	
1807	50	1807	50	Processing fee under 37 CFR 1.17(q)	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	770	2809	385	Filing a submission after final rejection (37 CFR 1.129(a))	
1810	770	2810	385	For each additional invention to be examined (37 CFR 1.129(b))	
1801	770	2801	385	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	

Other fee (specify) _____

*Reduced by Basic Filing Fee Paid

SUBTOTAL (3) ($) 330.00

SUBMITTED BY

(Complete *(if applicable)*)

Name *(Print/Type)*	Cynthia G. Tymeson	Registration No. *(Attorney/Agent)*	34,745	Telephone	302-631-0360
Signature	Cynthia G. Tymeson			Date	09/09/04

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Staples et al.	)	
	)	
Serial No.: 09/542,445	)	Art Unit: 1645
	)	
Date Filed: 04/04/00	)	Examiner: S. Devi, Ph.D.
	)	
Title: Reagents for Assays for Ligands	)	Date: September 9, 2004
	)	
Atty. Docket No.: BEH-7354A DIV	)	

The Honorable Commissioner of
Patents and Trademarks
Washington D.C. 20231

APPEAL BRIEF

Sir:

This is an appeal from the decision of the examiner to the Board of Patent Appeals and Interferences. The Notice of Appeal was filed on January 26, 2004 in response to a final rejection dated July 8, 2003, a Petition to Revive having been also filed on January 26, 2004, such petition being granted on July 9, 2004. The Appeal Brief is now due.

1. Real Party in Interest. The real party in interest in this appeal is the assignee of the application, Dade Behring Inc.

2. Related Appeals and Interferences. Applicants submit that there are no appeals or interferences currently pending or presently intended that will directly affect, or be directly affected by, or have a bearing on the Board's decision in this appeal.

3. Status of Claims. Claims 1-39 were filed in the parent case on July 17, 1997 as 08/896,244. Claims 4-39 were canceled without prejudice on April 25, 2000 and have been pursued in divisional applications.

Claim 1 was amended on January 2, 2002 to overcome a 102(e) rejection under Khanna et al.(US4798804) referred to herein as Khanna. Claim 1 was amended and the rejection was withdrawn on 04/05/2002, but the Examiner issued a new and final rejection of claims 1-3 under 103(a) in view of Nishijo *et al.* (*Chem. Pharm. Bull,* 33:2648-2653, 1985), or Kaufman (CA 2014233) in view of Neumann *et al.* (US 4559291) or Khanna. Applicants filed an RCE on September 30, 2002 which included arguments for patentability of claims 1-3 over the cited art. The Examiner withdrew the rejection on 12/31/02 but rejected the claims over Tabachnick *et al.* (*Arch. Biochem. Biophys.* 136: 467-479, 1970 and referred to herein as Tabachnick) in view of Khanna. Claims 1-3 were finally rejected on this same basis on July 08, 2003. A Reply was filed on

November 20, 2003 which contained arguments for patentability and included two terminal disclaimers to over come double-patenting rejections. Applicants believe that Reply was not entered, thus issues of double patenting remain but are not a subject of this appeal.

Claims 1-3 are the subject of this appeal and stand rejected under 35 U.S.C. §103 as being unpatentable over over Tabachnick in view of Khanna.

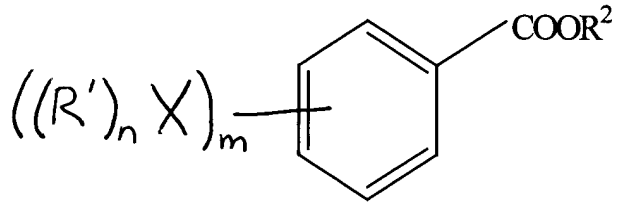
4. Status of Amendments. Claim 1 now on appeal was last amended on January 2, 2002. Claims 2 and 3 have not been amended. The claims are set out in Appendix 1.

5. Summary of the Invention. The subject matter claimed in the present application is useful in the field of assays of ligands including drug-ligands to provide a more accurate measurement of the ligand. When the ligand is being assayed it is often called the ligand analyte. Specification, page 1, lines 1-14 and page 6, lines 12 to page 8, line 16. Assays often rely on the binding of the ligand to a specific receptor for that ligand. Specification, page 1, lines 1-14. Samples taken from the body such as blood or urine often have substances, such as proteins, which interfere with that specific binding. Specification,

page 1, lines 26-29. Interference is caused by the endogenous protein binding non-specifically to the ligand thus inhibiting the ability of the ligand to bind to the specific receptor. These endogenous proteins which are often in high concentrations relative to the analyte can then bind to a significant number of analyte molecules and reduce the assay's sensitivity to the analyte. Specification page 1, lines 26-32.

In particular the claims provide a method which uses a releasing agent to diminish or remove the effect of interfering endogenous proteins (Specification page 10, line 30 to page 11, line 2) without some of the deficiencies of releasing agents previously used to release a ligand from an endogenous protein.

The medium which is suspected of having a complex of a ligand complexed to an endogenous protein is contacted with an effective amount of a compound having the following structure:



where R^2 is an alkyl group or H, R^1 is alkyl; X is O, S or N. When X is O or S, n is 1. When X is N, then n is 2. M(m) is 1 or 2. Specification page 4, lines 19-29.

In claim 2, X is O. In claim 3 the releasing agent used to release the ligand from the endogenous protein is methoxybenzoic acid.

6. Issue on Appeal. Whether or not claims 1-3 are unpatentable under 35 U.S.C. §103 over Tabachnick in view of Khanna?

7. Grouping of claims. There is a single rejection being appealed which applies to all claims. Applicants understand and acknowledge that the claims shall stand or fall together.

8. Arguments. Claims 1-3 stand rejected as being unpatentable under 35 U.S.C. §103 over Tabachnick in view of Khanna. The rejection is respectfully traversed.

The feature relied upon for novelty is the use of the particular releasing agents for releasing a ligand from a complex of a ligand with an endogenous protein. Use of these compounds to release a ligand from a complex of a ligand with an endogenous protein are neither disclosed nor suggested by Tabachnick in view of Khanna. Thus, it is applicants' position that the present invention is patentable over Tabachnick in view of Khanna.

The Examiner, in the Office Action dated 12/31/2002 at page 4, points to (a) the Abstract, (apparently the fourth sentence, which states " The effect of different substituents on the binding of phenols was in the order: alkyl group (CH_3-, or $(CH_3)_2C$-),< NO_2, Cl < Br, I." ,) (b) Table I (relating to phenols, not benzoates), (c) Table IV, (d) Figure 5 and (e) page 476 and 478, and states Tabachnick teaches a method for releasing a ligand (specifically thyroxine) from an endogenous protein (specifically albumin) using an *ortho* substituted benzoic acid derivative which contains an alkyl group. The Examiner then states that Khanna discloses that methoxybenzoic acid can be a releasing agent for releasing a ligand from a complex.

The Examiner concludes that it would be *prima facie* obvious for one skilled in the art to replace Tabachnick's *ortho* substituted alkyl containing benzoic acid releasing agent with Khanna's specific releasing agent, *para*-methoxy benzoic acid (see Khanna col. 3, lines 41-57, particularly line 57), to provide the method of this invention.

The Examiner states that " substitution of one substituted benzoic acid releasing agent with an alternate art-known specific benzoic acid releasing agent would have been well within the realm of routine experimentation and would have been obvious to one of skill in the art, since the latter was already taught

by Khanna *et al.* to serve as a conventionally used releasing agent" . See Office Action, 12/31/02 at page 4, next to the last paragraph.

Applicants would agree that Tabachnick tested several benzoic acid derivatives, some of which are *ortho*-substituted (among other derivatives), but Applicants disagree that Tabachnick teaches that any *ortho*-substituted benzoate containing an alkyl or *ortho* substituted derivatives are useful. In addition, the portion of the Abstract that mentions CH_3 as the least favorable substituent relates to <u>phenols</u> not benzoate. Table II also relates to phenols. Further, neither Table IV, Fig. 5, nor the pages referenced by the Examiner contain any benzoate substituted with CH_3 or recommend using an *ortho* substituted benzoate containing an alkyl.

Instead Tabachnick recommends extensive substitution by halogens (see Table II at page 471) but <u>not</u> at the ortho position (see abstract, page 471 col. 1 last sentence continuing to col. 2 and page 474, col. 2, first two full paragraphs). Instead Tabachnick recommends extensive substitution by halogens (or sometimes nitro) at the 3, 4, 5; or 3 and 5; or 2,3,5 positions as effective mainly to cause planarity of the molecule. See Table II at page 471, Table IV at page 472, and page 474, col. 2, first full paragraph, second sentence. In fact, Tabachnick teaches that *ortho*

positions are inhibitory - which can be overcome by adding halogens - page 474, col.2, full paragraph.

Thus, Applicants assert that one skilled in the art would not read Tabachnick as teaching *ortho* substituted benzoic acid derivatives which contain an alkyl group are useful releasing agents. In fact, Applicants submit that Tabachnick directs one skilled in the art away from derivatives which do not contain halogen or nitro groups, particularly these groups at the 3, 4, 5; or 3 and 5; or 2,3,5 positions. Thus, one would not look to Khanna which discloses *para*-methoxybenzoic acid to release cylcodextrin (a carbohydrate, not an endogenous protein) from digoxin(a ligand).

Further, Khanna specifically discloses that the ring is unsubstituted at the 2,3,5 and 6 positions, contrary to Tabachnick which teaches particularly halogen substituents and particular substitutions at 3, 4, 5; or 3 and 5; or 2,3,5 positions. See Khanna, col. 3, lines 40 - 47.

Even if one were to look at Khanna, Khanna does not disclose compounds for releasing endogenous proteins from ligands. Instead Khanna discloses a process to determine the presence of digoxin with a first step of binding digoxin to cyclodextrin, a carbohydrate and then releasing the cyclodextrin from the digoxin using in one instance a methoxybenzoic

acid. There is no suggestion that this releasing agent would work for complexes other than cyclodextin:digoxin let alone for any complex which includes endogenous proteins. Nor does Tabachnick provide even a suggestion to try Khanna's derivative or does Khanna suggest that the disclosed releasing agents might work with releasing endogenous proteins.

Nowhere does Tabachnick, even in combination with Khanna, discuss, teach, or even suggest that the compounds of claim 1 or methoxybenzoic acid would be useful for releasing ligands from endogenous proteins. This feature is fully disclosed, taught and claimed by Applicants.

Thus, applicants contend that the combination does not teach or suggest the present invention.

For all of the foregoing reasons, Applicants respectfully request that the rejection be withdrawn and that the claims be allowed to issue.

Respectfully submitted,

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Reg. No. 34,745

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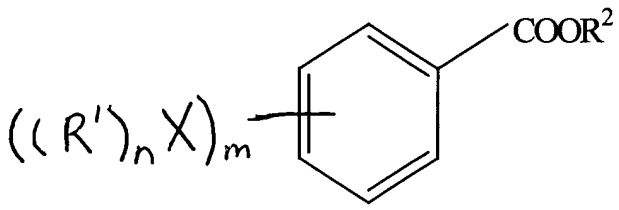
APPENDIX 1

Claim 1 (as amended). A method for releasing a ligand from a complex with endogenous proteins, said method comprising contacting a medium suspected of containing said complex with an effective amount of a compound of the formula:



wherein R^1 is alkyl; R^2 is hydrogen or alkyl; X is O, S or N; n is 1 when X is O or S and n is 2 when X is N; and m is 1 or 2.

Claim 2. The method of Claim 1 wherein X is O.

Claim 3. The method of Claim 1 wherein said compound is methoxybenzoic acid.